Subject: Hematopoietic Stem Cell Transplantation for Acute Lymphoblastic Leukemia (ALL)	Original Effective Date: 10/31/2012
Policy Number: MCP-118	**Revision Date(s):** 7/29/2015
Review Date: 12/16/15, 12/14/16, 6/22/17	

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina Clinical Policy (MCP) document and provide the directive for all Medicare members.[1]

DESCRIPTION OF PROCEDURE/SERVICE/PHARMACEUTICAL

Acute Lymphoblastic Leukemia

Acute leukemia's comprise a heterogeneous group of neoplastic disorders that arise from malignant transformation of blood-forming, or hematopoietic, stem cells. Malignant transformation typically involves chromosomal rearrangements (translocations), deletions, or additions, which disturb the normal control of cell division, allowing affected cells to multiply without restraint. Clones, or leukemic cells, arising from such transformation particularly influence the development of white blood cells (WBCs), or leukocytes, and rapidly proliferate in the bone marrow, ultimately replacing normal cells and causing anemia, thrombocytopenia, and granulocytopenia. After release into the blood stream, leukemic cells can infiltrate any organ or site and often spread to the liver, spleen, lymph nodes, central nervous system (CNS), and gonads, where they continue to grow and divide, resulting in small tumors, inflammation, and/or organ damage and failure. One of two major types of acute leukemia, acute lymphoblastic leukemia (ALL) involves stem cells that normally become lymphoblasts, the precursors of leukocytes known as lymphocytes and is an aggressive type of leukemia characterized by the presence of too many lymphoblasts or lymphocytes in the bone marrow and peripheral blood. It can spread to the lymph nodes, spleen, liver, central nervous system (CNS), and other organs. Without treatment, ALL usually progresses quickly. ALL occurs in both children and adults and it is the most common type of cancer in children. ALL is believed to arise from malignant transformation of B- or T-cell progenitor cells. It is more commonly seen in children, but can occur at any age. The disease is characterized by the accumulation of lymphoblasts in the marrow or in various extramedullary sites. The World Health Organization (WHO) classifies ALL as either B lymphoblastic leukemia or T lymphoblastic leukemia. B lymphoblastic leukemia is subdivided by the presence or absence of specific recurrent genetic abnormalities (t(9;22)), MLL

rearrangement, t(12;21), hyperdiploidy, hypodiploidy, t(5;14), and t(1;19). Current treatment decisions rely on the immunophenotype (early-pre-B ALL, pre-B ALL, B-cell ALL, or T-cell ALL) and cytogenetics of affected cells. Hematopoietic stem cells transplantation is a treatment method provided to patients with leukemia disorders to rescue the patients from treatment-induced aplasia after high-dose chemotherapy and/or radiotherapy has been administered to eliminate the recipient's immune system. [22 26]

Stem Cell Transplantation

Stem-cell transplantation refers to transplantation of hematopoietic stem cells (HSCs) from a donor into a patient. HSCs are immature cells that can develop into any of the three types of blood cells (red cells, white cells or platelets). HSCs are created in the bone marrow and are found in the bone marrow and peripheral blood. There is also a high concentration of HSCs in umbilical-cord blood. Hematopoietic stem-cell transplantation (HSCT) can be either autologous (using the person's own stem cells) or allogeneic (using stem cells from a donor). In allogeneic HSCT, it is preferable for donors to have a human leukocyte antigen (HLA) type that is identical to the recipient. Matching is performed on the basis of variability at three of more loci of the HLA gene (e.g., HLA-A, HLA-B, HLA-DRB1). As HLA variability increases, transplant-related morbidity and mortality, including graft rejection and graft-versus-host disease, also increase. [14]

In general, transplants in first remission have a better chance of a good outcome than transplants received later or when the disease is not in remission. For adults, a transplant in first complete remission or early disease offers a higher likelihood of 5-year survival compared to transplants for patients in second remission or with advanced disease. For children the likelihood of 5-year survival is increased for patients who receive a transplant in early or intermediate disease or first or second complete remission compared to patients with advanced disease at the time of transplant. [2]

RECOMMENDATION [1 3 15 16 23-32]

All transplants require prior authorization from the Corporate Transplant Department. Solid organ transplant requests will be reviewed by the Corporate Senior Medical Director or qualified clinical designee. All other transplants will be by the Corporate Senior Medical Director or covering Medical Director. If the criteria are met using appropriate NCD and/or LCD guidelines, state regulations and/or MCP policies the Corporate Senior Medical Director's designee can approve the requested transplant.

Members must meet UNOS guidelines for transplantation and the diagnosis must be made by a *Specialist in the Disease* and or Transplant Surgeon.

Pre-Transplant Evaluation: [23 31]

Criteria for transplant evaluation include all of the following:

- ❑ History and physical examination
- ❑ Psychosocial evaluation and clearance:
  - o No behavioral health disorder by history or psychosocial issues:
    - ➢ if history of behavioral health disorder, no severe psychosis or personality disorder
    - ➢ mood/anxiety disorder must be excluded or treated

- member has understanding of surgical risk and post procedure compliance and follow-up required
- Adequate family and social support

- ❑ EKG
- ❑ Chest x-ray
- ❑ Cardiac clearance in the presence of any of the following:
  - chronic smokers
  - > 50 years age
  - those with a clinical or family history of heart disease or diabetes
- ❑ Pulmonary clearance if evidence of pulmonary artery hypertension (PAH) or chronic pulmonary disease
- ❑ Neurological exam and clearance for transplant: [ONE]
  - Normal exam by H&P
  - Abnormal neurological exam with positive findings: [ONE]
    - Lumbar puncture normal cytology
    - Lumbar puncture with cytological exam abnormal: CNS disease treated prior to clearance
- ❑ Performance Status : [ONE]
  - Karnofsky score 70-100%; or
  - Eastern Cooperative Oncology Group (ECOG) grade 0-2
- ❑ Lab studies:
  - *Complete blood count, Kidney profile (blood urea nitrogen, creatinine), electrolytes, calcium, phosphorous, albumin, liver function tests, Coagulation profile (prothrombin time, and partial thromboplastin time)
  - *Serologic screening for HIV, Epstein Barr virus (EBV), Hepatitis virus B (HBV), and Hepatitis C(HCV), cytomegalovirus (CMV), RPR and/or FTA:
    - If HIV positive all of the following are met:
      - CD4 count >200 cells/mm-3 for >6 months
      - HIV-1 RNA undetectable
      - On stable anti-retroviral therapy >3 months
      - No other complications from AIDS (e.g., opportunistic infection, including aspergillus, tuberculosis, coccidioides mycosis, resistant fungal infections, Kaposi's sarcoma, or other neoplasm)
    - If abnormal serology need physician plan to address and/or treatment as indicated
  - UDS (urine drug screen) if patient is current or gives a history of past drug abuse
- ❑ *Colonoscopy (if indicated or if patient is 50 ≥ older should have had an initial screening colonoscopy, after initial negative screening requires follow up colonoscopy every ten years) with complete workup and treatment of abnormal results as indicated
- ❑ *GYN examination with Pap smear for women ≥ 21 to ≤ 65 years of age or indicated (not indicated in women who have had a TAH or TVH) with in the last three year with complete workup and treatment of abnormal results as indicated

Within the last 12 months:

- ❑ Dental examination or oral exam showing good dentition and oral care or no abnormality on panorex or plan for treatment of problems pre or post-transplant

- ❑ *Mammogram (if indicated or > age 40) with complete workup and treatment of abnormal results as indicated
- ❑ *PSA if history of prostate cancer or previously elevated PSA with complete workup and treatment of abnormal results as indicated

Participating Centers of Excellence may waive these criteria

Criteria for Hematopoietic Allogeneic Stem Cell transplantation (HSCT) Transplantation:

1. ***Hematopoietic Allogeneic stem-cell transplantation (HSCT)*** *ablative or non-myeloablative* from a human leukocyte antigen (HLA)-matched donor (i.e., at least six out of eight match of the HLA-A, HLA-B, HLA-C and HLA-DRB1 markers) or from cord blood when there are no matched sibling or unrelated donors (i.e. at least four out of six match of the HLA-A, HLA-B and HLA-DRB-1 markers) is considered medically necessary and may be authorized for the treatment of acute lymphocytic/lymphoblastic leukemia (ALL) when ANY of the following criteria are met: **[ONE]**

   - ❑ All pre-transplant criteria are met; and

   - ❑ Failed induction: presence of leukemia blasts in the blood, bone marrow or any extramedullary site after 4-6 weeks of initiation of therapy; or

   - ❑ Complete first remission (CR-1) defined by bone marrow biopsy as **[BOTH]**: [26 31]

     - bone marrow is normocellular with no more than 5% blasts; and
     - no signs or symptoms of the disease

     AND

   - ❑ In ***adults*** who are > age 18 and ***children*** who are < age 18 with any of the following high risk factors for relapse**[ONE]**:
     - longer than six weeks to achieve a complete remission
     - high white blood cell count (WBC) > 50,000 at diagnosis
     - extramedullary disease outside the bone marrow especially affecting central nervous system
     - positive Philadelphia chromosome: (t(9;22) or BCR-ABL positive)
     - any of the following chromosome abnormalities: t(4;11), t(1;19), t(8;14), deletion of(7q), trisomy 8, 11q23 (MLL) translocation
     - hypodiploidy: defined as less than 45 chromosomes
     - presence of Mature B cell phenotype (Burkitt's lymphoma)
     - children who are < 1 year or > 9 years [26 31]
     - adults who are < 35 years [26 31]

     OR

- ❑ Second or subsequent complete remission (CR-2) following complete first remission (CR-1) defined by bone marrow biopsy as **[BOTH]**: [26 31]
    - bone marrow is normocellular with no more than 5% blasts; and
    - no signs or symptoms of the disease

OR

- ❑ Any stage of relapse [23]

AND

- ❑ The requesting transplant recipient should not have any of the following **absolute contraindications**:
    - Cardiac, pulmonary, and nervous system disease that cannot be corrected and is a prohibitive risk for surgery
    - Malignant neoplasm with a high risk for reoccurrence, non-curable malignancy (excluding localized skin cancer)
    - Systemic and/or uncontrolled infection
    - AIDS (CD4 count < 200cells/mm3)
    - Unwilling or unable to follow post-transplant regimen
        - ◊ Documented history of non-compliance
        - ◊ Inability to follow through with medication adherence or office follow-up
    - Chronic illness with one year or less life expectancy
    - Limited, irreversible rehabilitation potential
    - Active untreated substance abuse issues, requires documentation supporting free from addiction for minimally 6 months if previous addiction was present
    - No adequate social/family support

- ❑ The requesting transplant recipient should be evaluated carefully and potentially treated if the following **relative contraindications** are present:
    - Irreversible lung disease patients require consultation and clearance by a Pulmonologist prior to consideration of transplantation, this includes the following:
    - Smoking, documentation supporting free from smoking for 6 months
    - Active peptic ulcer disease
    - Active gastroesophageal reflux disease
    - CVA with long term impairment that is not amendable to rehabilitation or a patient with CVA/transient ischemic attack within past 6 months
    - Obesity with body mass index of >30 kg/m^2 may increase surgical risk
    - Chronic liver disease such as Hepatitis B/C/D, or cirrhosis which increases the risk of death from sepsis and hepatic failure requires consultation by a gastroenterologist or hepatologist
    - Gall bladder disease requires ultrasound of the gall bladder with treatment prior to transplantation

Criteria for Hematopoietic Autologous Stem Cell Transplantation:

2. - ***Hematopoietic Autologous stem cell transplantation*** may be authorized **only if** the member has acute lymphocytic/lymphoblastic leukemia **and:**

   - ❑ All pre-transplant criteria are met; and
   - ❑ Does not have an allogeneic donor **or** has medical contraindications to an allogeneic transplantation procedure; **and**
   - ❑ Is in morphologic and cytogenetic complete remission (CR) at the time of stem cell harvest; and
   - ❑ Should not have any of the absolute contraindications and should be evaluated for any relative contraindications listed above

Criteria for Subsequent Hematopoietic Stem Cell Transplantation:

3. ***Hematopoietic Allogeneic Stem Cell Transplantation*** *(ablative or non-myeloablative)* may be authorized after the *first prior autologous stem cell transplantation* has occurred only one time, for members with acute lymphocytic/lymphoblastic leukemia who meet all of the above criteria for transplant and have any of the following:**[ONE]**

   - ❑ bone marrow relapse: defined as the reappearance of leukemia cells in the bone marrow or peripheral blood after a complete remission as indicated by a peripheral blast count of 5,000 or greater; or
   - ❑ primary graft failure indicated by no signs of engraftment* by 42 days after the transplant; or
   - ❑ failure to engraft*;

   AND

   - ❑ a suitable allogeneic donor has been identified

4. ***Hematopoietic Autologous or Allogeneic stem cell transplantation*** *(ablative or non-myeloablative)* may be authorized after *the first prior stem cell transplantation* has occurred only one time for members with acute lymphocytic/lymphoblastic leukemia who meet all of the above criteria for transplant and have any of the following**:[ONE]**

   - ❑ bone marrow relapse: defined as the reappearance of leukemia cells in the bone marrow; or peripheral blood after a complete remission as indicated by a peripheral blast count of ≥ 5,000; or
   - ❑ primary graft failure indicated by no signs of engraftment* by 42 days after the transplant;

   OR

   - ❑ failure to engraft*;

   AND

   - ❑ a suitable allogeneic donor has been identified if applicable

***Note:** Engraftment is defined as the first 3 consecutive days on which the absolute neutrophil count (ANC) exceeds 5 x 10^9/L or > ANC500at any time after transplantation.*[27]

CONTINUATION OF THERAPY

When extension of a previously approved transplant authorization is requested, review using updated clinical information is appropriate.

- ❑ If Molina Healthcare has authorized prior requests for transplantation, the following information is required for medical review: [ALL]
  - Presence of no absolute contraindication as listed above;
  - History and physical within the last 12 months;
  - Kidney profile within the last 12 months;
  - Cardiac update if history of cardiac disease within two years (≥ 50 years of age);
  - Psychosocial evaluation or update within the last 12 months;
  - Per initial and updated history and physical, any other clinically indicated tests and/or scans as determined by transplant center physician or Molina Medical Director.

- ❑ If authorized prior requests for transplantation were obtained from another insurer, the following information is required for medical review: [ALL]
  - Authorization letter/documentation from previous insurer;
  - Presence of no absolute contraindication as listed above;
  - History and physical within the last 12 months;
  - Cardiac update if history of cardiac disease within two years (≥ 50 years of age);
  - Psychosocial evaluation or update within the last 12 months;
  - Per initial and updated history and physical, any other clinically indicated tests and/or scans as determined by transplant center physician or Molina Medical Director.

COVERAGE EXCLUSIONS

1. Allogeneic (ablative or non-myeloablative) stem cell transplantation or autologous stem cell transplantation when the above criteria are not met.
2. A second or repeat autologous or allogeneic (ablative or non-myeloablative) transplant due to persistent, progressive disease
3. Hematopoietic stem cell collection, storage and freezing for a future unplanned transplant

SUMMARY OF MEDICAL EVIDENCE [2 4-22]

The published medical evidence and outcomes for hematopoietic stem cell transplantation for acute lymphoblastic leukemia (ALL) in children and adults in the United States consists of registry data obtained from transplant centers that perform adult and pediatric transplantation and is available from the United Network for Organ Sharing (UNOS) database. Registry data demonstrates graft survival rates and outcomes for stem cell transplantation based on demographic and clinical information. [2]

Adults:

In 2011, Pidala et al published a Cochrane systematic review of randomized controlled trials comparing the effect of matched sibling donor vs. no donor status for adults with ALL in first complete remission (CR1). A total of 14 relevant trials were identified, consisting of a total of 3157 patients. Matched sibling donor

allogeneic SCT was superior CR1 therapy in ALL patients aged 15 years or over for overall survival (p=0.01), disease-free survival (p = 0.004), and reduced relapse risk (p=0.0004). The authors cautioned that "these data are based on adult ALL treated with largely total body irradiation-based myeloablative conditioning and sibling donor transplantation and, therefore, cannot be generalized to pediatric ALL, alternative donors including HLA (human leukocyte antigen) mismatched or unrelated donors, or reduced toxicity or non-myeloablative conditioning regimens. [5]

A systematic review and meta-analysis of randomized trials, including patients with standard-risk (SR) All and high-risk (HR) ALL who received first postremission therapy was conducted to compare the various potential therapeutic options for patients who achieved first complete remission. Outcomes assessed were all-cause mortality (ACM), disease recurrence (relapse), and nonrelapse mortality (NRM). Relative risks (RRs) with 95% confidence intervals (CIs) were estimated and pooled. The results showed that there was a significant reduction in ACM in the allogeneic stem cell transplantation (alloSCT) arm (RR, 0.88; 95% CI, 0.8-0.97) compared with autologous stem cell transplantation (ASCT) or chemotherapy. Subgroup analyses revealed a similar pattern among SR patients (RR, 0.8; 95% CI, 0.68-0.94) but a nonsignificant advantage for alloSCT among HR patients (RR, 0.88; 95% CI, 0.76-1.01). There was an increase in NRM (RR, 2.99; 95% CI, 1.37-6.53) and a decrease in the relapse rate in the alloSCT arm (RR, 0.52; 95% CI, 0.33-0.83). There was no difference in ACM or the relapse rate between the ASCT and chemotherapy arms. The authors concluded that alloSCT was superior to ASCT or chemotherapy for patients with ALL in first complete remission. The survival advantage was of greater statistical significance for patients with SR ALL than for patients with HR ALL. [6]

Children:

A review of failure of remission-induction therapy in children and adolescents with acute lymphoblastic leukemia (ALL) was conducted. Induction failure was defined as the persistence of leukemic blasts in blood, bone marrow, or any extramedullary site after 4 to 6 weeks of remission-induction therapy. The relationships among disease characteristics, treatments administered, and outcomes were evaluated in a total of 1041 of 44,017 patients (2.4%) 0 to 18 years of age with newly diagnosed ALL who were treated by a total of 14 cooperative study groups between 1985 and 2000. The results showed that patients with induction failure frequently presented with high-risk features, including older age, high leukocyte count, leukemia with a T-cell phenotype, the Philadelphia chromosome, and 11q23 rearrangement. With a median follow-up period of 8.3 years (range, 1.5 to 22.1), the 10-year survival rate (±SE) was estimated at only 32±1%. An age of 10 years or older, T-cell leukemia, the presence of an 11q23 rearrangement, and 25% or more blasts in the bone marrow at the end of induction therapy were associated with a particularly poor outcome. High hyperdiploidy (a modal chromosome number >50) and an age of 1 to 5 years were associated with a favorable outcome in patients with precursor B-cell leukemia. Allogeneic stem-cell transplantation from matched, related donors was associated with improved outcomes in T-cell leukemia. Children younger than 6 years of age with precursor B-cell leukemia and no adverse genetic features had a 10-year survival rate of 72±5% when treated with chemotherapy only. The authors concluded that pediatric ALL with induction failure is highly heterogeneous. Patients who have T-cell leukemia appear to have a better outcome with allogeneic stem-cell transplantation than with chemotherapy, whereas patients who have precursor B-cell leukemia without other adverse features appear to have a better outcome with chemotherapy. [7]

A review was conducted to examine population-based improvements in survival and the impact of clinical covariates on outcome among children and adolescents with acute lymphoblastic leukemia (ALL) enrolled onto Children's Oncology Group (COG) clinical trials between 1990 and 2005. A total of 21,626 persons age 0 to 22 years were enrolled onto COG ALL clinical trials from 1990 to 2005, representing 55.8% of ALL cases estimated to occur among US persons younger than age 20 years during a period divided into three eras (1990-1994, 1995-1999, and 2000-2005). 5- and 10-year survival over time and the relationship of those changes in survival to clinical covariates, with additional analyses of cause of death were examined. The results showed that five-year survival rates increased from 83.7% in 1990-1994 to 90.4% in 2000-2005 ($P < .001$). Survival improved significantly in all subgroups (except for infants age ≤ 1 year), including males and females; those age 1 to 9 years, 10+ years, or 15+ years; in whites, blacks, and other races; in Hispanics, non-Hispanics, and patients of unknown ethnicity; in those with B-cell or T-cell immunophenotype; and in those with National Cancer Institute (NCI) standard- or high-risk clinical features. Survival rates for infants changed little, but death following relapse/disease progression decreased and death related to toxicity increased. The authors concluded that this study documents ongoing survival improvements for children and adolescents with ALL. Thirty-six percent of deaths occurred among children with NCI standard-risk features emphasizing that efforts to further improve survival must be directed at both high-risk subsets and at those children predicted to have an excellent chance for cure. [8]

Autologous vs. Allogeneic Stem Cell Transplant:

A systematic overview of the best available evidence on the clinical effectiveness and cost-effectiveness of SCT in the treatment of acute leukemia was conducted. Electronic databases, including MEDLINE, EMBASE and the Cochrane Library, were searched from inception to December 2008 to identify published systematic reviews and meta-analyses. reviews and meta-analyses were critically appraised and data extracted and narratively presented. Included randomized controlled trials (RCTs) and donor versus no donor (DvND) studies were mapped to the evidence covered in existing systematic reviews and meta-analyses according to a framework of 12 decision problems (DPs): DP1 related to SCT in adults with AML in first complete remission (CR1); DP2 to adults with AML in second or subsequent remission or with refractory disease (CR2+); DP3 to children with AML in CR1; DP4 to children with AML in CR2+; DP5 to adults with ALL in CR1; DP6 to adults with ALL in CR2+; DP7 to children with ALL in CR1; DP8 to children with ALL in CR2+; DP9 to comparison of different sources of stem cells in transplantation; DP10 to different conditioning regimens; DP11 to the use of purging in autologous SCT; and DP12 to the use of T-cell depletion in allogeneic SCT. Fifteen systematic reviews/meta-analyses met the inclusion criteria for the review of clinical effectiveness, thirteen of which were published from 2004 onwards. The best available evidence for effectiveness of allogeneic SCT using stem cells from matched sibling donors came from DvND studies: there was sufficient evidence to support the use of allogeneic SCT in DP1 (except in good-risk patients), DP3 (role of risk stratification unclear) and DP5 (role of risk stratification unclear). There was conflicting evidence in DP7 and a paucity of evidence from DvND studies for all decision problems concerning patient groups in CR2+. The best available evidence for effectiveness of autologous SCT came from RCTs: overall, evidence suggested that autologous SCT was either similar to or less effective than chemotherapy. There was a paucity of evidence from published reviews of RCTs for DPs 9-12. Nineteen studies met the inclusion criteria in the cost-effectiveness review, most reporting only cost information and only one incorporating an economic model. Although there is a wealth of information on costs and some

information on cost-effectiveness of allogeneic SCT in adults with AML (DPs 1 and 2), there is very limited evidence on relative costs and cost-effectiveness for other DPs. The authors concluded that existing evidence suggests that sibling donor allogeneic SCT may be more effective than chemotherapy in adult AML (except in good-risk patients) in CR1, childhood AML in CR1 and adult ALL in CR1, and that autologous SCT is equal to or less effective than chemotherapy. [9]

A review of hematopoietic cell transplantation (HCT) for high-risk or recurrent acute lymphoblastic leukemia (ALL) using different donor sources was conducted. A total of 623 consecutive ALL myeloablative HCT (1980 to 2005) were reviewed. Donors were autologous (n = 209), related (RD; n = 245), unrelated (URD; n = 100), and umbilical cord blood (UCB; n = 69). The results showed that after median of 8.3 years of follow-up, 5-year overall survival (OS), leukemia-free survival (LFS), and relapse were 29% ,26% and 43%, respectively. Treatment-related mortality (TRM) at 2 years was 28%. Mismatched URD sources yielded higher TRM and lower OS than RD or UCB HCT. Autografting yielded significantly more relapse and poorer LFS. HCT in first complete remission (CR1) yielded significantly better outcomes than later HCT. In a 1990 to 2005 allogeneic CR1/second complete response cohort, 5-year OS, LFS, and relapse rates were 41%, 38% (95% CI, 32% to 44%), and 25% respectively; 2-year TRM was 34%. With RD, well-matched URD and UCB sources, 5-year LFS was 40% 42% and 49% respectively, while relapse was 31% 17% , and 27% .Acute graft-versus-host disease was associated with fewer relapses. Since 1995 progressive improvements in OS, LFS, and TRM were noted. The authors concluded that allogeneic, but not autologous, HCT for ALL results in durable LFS. Importantly, HCT using UCB led to similar outcomes as either RD or well-matched URD. HCT in early remission can best exploit the potent antileukemic efficacy of allografting from UCB, RD, or URD sources. [10]

The GOELAL02 trial evaluated the impact of early allogeneic bone marrow transplantation (alloBMT) or delayed unpurged autologous stem cell transplantation (ASCT) for patients who had no human leukocyte antigen (HLA)–matched sibling donor or who were older than 50 years. Inclusion criteria included at least one of the following: age older than 35 years; non–T-ALL; leukocytosis greater than 30×10^9/L; t(9;22), t(4;11), or t(1; 19); or failure to achieve complete remission (CR) after one induction course. Among 198 patients, the median age was 33 years. The CR rate was 80% with vincristine, idarubicine, L-asparaginase, and randomized intravenous injection or oral steroids. AlloBMT was performed after 2 consolidation courses while ASCT was delayed after 1 additional reinduction. Intensified conditioning regimen before transplantation included etoposide, cyclophosphamide, and total body irradiation (TBI). Median follow-up was 5.1 years. The median overall survival (OS) was 29 months, with a 6-year OS of 41%. On an intent-to-treat analysis for patients younger than 50 years, alloBMT significantly improved the 6-year OS (75% versus 40% after ASCT. Randomized interferon-α maintenance had no effect on relapse or survival after ASCT. The authors concluded that the outcome of adult ALL is better after early alloBMT than after delayed ASCT. [11]

The International ALL trial was set up to prospectively evaluate the role of allogeneic transplantation for adults with acute lymphoblastic leukemia (ALL) and compare autologous transplantation with standard chemotherapy. Patients received 2 phases of induction and, if in remission, were assigned to allogeneic transplantation if they had a compatible sibling donor. Other patients were randomized to chemotherapy for 2.5 years versus an autologous transplantation. A donor versus no-donor analysis showed that Philadelphia chromosome–negative patients with a donor had a 5-year improved overall survival (OS), 53% versus 45% ($P = .01$), and the relapse rate was significantly lower ($P \leq .001$). The survival difference was significant in standard-risk patients, but not

in high-risk patients with a high nonrelapse mortality rate in the high-risk donor group. Patients randomized to chemotherapy had a higher 5-year OS (46%) than those randomized to autologous transplantation (37%; *P* = .03). The authors concluded that matched related allogeneic transplantations for ALL in first complete remission provide the most potent antileukemic therapy and considerable survival benefit for standard-risk patients. However, the transplantation-related mortality for high-risk older patients was unacceptably high and abrogated the reduction in relapse risk. There is no evidence that a single autologous transplantation can replace consolidation/maintenance in any risk group. [12]

Professional Society Guidelines: Several professional society organizations have recommended that Allogeneic SCT is the preferred method of treatment for individuals in first complete remission (CR1) with HLA matched sibling donor, ALL after relapse, and second complete remission (CR2). [23-28]

- **The National Marrow Donor Program**: The NMDP recommends that adults age 15-39 years with high-risk CR1 ALL be referred for consultation for HSCT when the following characteristics are present: Philadelphia chromosome positive or Philadelphia-like, iAMP21or 11q23 rearrangement or B-cell with poor-risk cytogenetics. Also HSCT is recommended for the following: primary induction failure or relapse, presence of minimal residual disease after initial or subsequent therapy, CR2 and beyond, if not previously evaluated. The NMDP also recommends that infants and children up to age 15 years at diagnosis with high-risk CR1 ALL be referred for consultation for HSCT when one of the following characteristics is present: induction failure, Philadelphia chromosome positive, 11q23 or iAMP21 rearrangement, mature B-cell phenotype (Burkitt's lymphoma), and primary induction failure or relapse, presence of minimal residual disease after initial or subsequent therapy, CR2 and beyond, if not previously evaluated. [23]
- **NCCN Clinical Practice Guidelines in Oncology (2018)** recommend allogenic transplant for patients with PH-positive ALL however, options are limited for those who relapse after transplant. Participation in clinical trials for adults with relapsed/refractory disease after an initial CR for individuals with Ph-negative ALL is recommended. In lieu of an appropriate trial, re-induction, salvage chemotherapy or allogeneic HSCT are recommended treatment options. [24]

CODING INFORMATION THE CODES LISTED IN THIS POLICY ARE FOR REFERENCE PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE.

CPT	Description
	Collection Codes
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38230	Bone marrow harvesting for transplantation; allogeneic
38232	Bone marrow harvesting for transplantation; autologous
	Cell Processing Services
38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage

38208	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing
38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing
38210	Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion
38211	Transplant preparation of hematopoietic progenitor cells; tumor cell depletion
38212	Transplant preparation of hematopoietic progenitor cells; red blood cell removal
38213	Transplant preparation of hematopoietic progenitor cells; platelet depletion
38214	Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion
38215	Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer
	Cell infusion codes
38240	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic
38241	Bone marrow or blood-derived peripheral stem cell transplantation; autologous
38242	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic donor lymphocyte infusions
38243	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic hematopoietic cellular transplant boost

HCPCS	Description
S2140	Cord blood harvesting for transplantation, allogeneic
S2142	Cord blood derived stem-cell transplantation, allogeneic
S2150	Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including pheresis and cell preparation/storage; marrow ablative therapy; drugs; supplies; hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre-and post-transplant care in the global definition

ICD-9	Description: [For dates of service prior to 10/01/2015]
204.00-204.02	Acute lymphoid leukemia

ICD-10	Description: [For dates of service on or after 10/01/2015]
C91.00- C91.92	Acute lymphoblastic leukemia

RESOURCE REFERENCES

Government Agency

1. Centers for Medicare & Medicaid Services. NCD for Stem Cell Transplantation (Formerly 110.8.1) 110.23. Effective date 1/27/2016. Accessed at: http://www.cms.gov/medicare-coverage-database/
2. National Marrow Donor Program. ALL Transplant Outcomes. Accessed at: http://marrow.org/Patient/Disease_and_Treatment/About_Your_Disease/ALL/Transplant_Results.aspx
3. National Bone Marrow Donor Program HLA Matching Requirements. Accessed at: http://marrow.org/Patient/Transplant_Process/Search_Process/HLA_Matching__Finding_the_Best_Donor_or_Cord_Blood_Unit.aspx

Peer Reviewed Publications

4. Yanada, M, Matsuo, K, Suzuki, T, Naoe, T. Allogeneic hematopoietic stem cell transplantation as part of postremission therapy improves survival for adult patients with high-risk acute lymphoblastic leukemia: a meta-analysis. *Cancer*. 2006 Jun 15;106(12):2657-63. PMID: 16703597 . Accessed at: http://onlinelibrary.wiley.com/doi/10.1002/cncr.21932/abstract
5. Pidala, J, Djulbegovic, B, Anasetti, C, Kharfan-Dabaja, M, Kumar, A. Allogeneic hematopoietic cell transplantation for adult acute lymphoblastic leukemia (ALL) in first complete remission. *Cochrane Database Syst Rev*. 2011(10):CD008818. PMID: 21975786
6. Ram R, Gafter-Gvili A et al. Management of adult patients with acute lymphoblastic leukemia in first complete remission: systematic review and meta-analysis. Cancer. 2010 Jul 15;116(14):3447-57. Accessed at: http://onlinelibrary.wiley.com/doi/10.1002/cncr.25136/abstract;jsessionid=27838E34E6BCC66B8FA82ECB1FB9A47D.d03t02
7. Schrappe M, Hunger SP et al. Outcomes after induction failure in childhood acute lymphoblastic leukemia. N Engl J Med. 2012 Apr 12;366(15):1371-81. Accessed at: http://www.nejm.org/doi/full/10.1056/NEJMoa1110169
8. Hunger SP, Lu X, Devidas M et al. Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the children's oncology group. J Clin Oncol. 2012 May 10;30(14):1663-9. Epub 2012 Mar 12.
9. Ashfaq K, Yahaya I et al. Clinical effectiveness and cost-effectiveness of stem cell transplantation in the management of acute leukaemia: a systematic review. Health Technol Assess. 2010 Dec;14(54):iii-iv, ix-xi, 1-141.
10. Tomblyn MB, Arora M, Baker KS et al. Myeloablative hematopoietic cell transplantation for acute lymphoblastic leukemia: analysis of graft sources and long-term outcome. J Clin Oncol. 2009 August 1; 27(22): 3634–3641. Accessed at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720079/?tool=pubmed
11. Hunault M, Harousseau JL, Delain M et al. Better outcome of adult acute lymphoblastic leukemia after early genoidentical allogeneic bone marrow transplantation (BMT) than after late high-dose therapy and autologous BMT: a GOELAMS trial. Blood. 2004 Nov 15;104(10):3028-37. Epub 2004 Jul 15.
12. Goldstone AH, Richards SM, Lazarus HM, et al. In adults with standard-risk acute lymphoblastic leukemia, the greatest benefit is achieved from a matched sibling allogeneic transplantation in first complete remission, and an autologous transplantation is less effective than conventional consolidation/maintenance chemotherapy in all patients: final results of the International ALL Trial (MRC UKALL XII/ECOG E2993). Blood. 2008; 111(4):1827-1833. Accessed at: http://dx.doi.org/10.1182/blood-2007-10-116582
13. Imrie K, Rumble RB, Crump M, Advisory Panel on Bone Marrow and Stem Cell Transplantation, Hematology Disease Site Group. Stem cell transplantation in adults: recommendations. Toronto (ON): Cancer Care Ontario Program in Evidence-based Care; 2009 Jan 30. 78 p. Accessed at: https://www.cancercare.on.ca/common/pages/UserFile.aspx?serverId=6&path=/File%20Database/CCO%20Files/PEBC/pebc_stemcell.pdf
14. C Mackall, T Fry, R Gress, K Peggs, J Storek and A Toubert. Background to hematopoietic cell transplantation, including post-transplant immune recovery. Bone Marrow Transplant 44: 457-462; doi:10.1038/bmt.2009.255 Accessed at: http://www.nature.com/bmt/journal/v44/n8/full/bmt2009255a.html
15. Eastern Cooperative Oncology Group (ECOG) Performance Status. Accessed at: http://www.ecog.org/general/perf_stat.html

16. Collins RH, Goldstein S, Giralt S, et al. Donor leukocyte infusions in acute lymphocytic leukemia. Bone Marrow Transplant. 2000; 26(5): 511-516. Accessed at: http://www.nature.com/bmt/journal/v26/n5/full/1702555a.html
17. Mackinnon S. American Society of clinical Oncology (ASCO). Donor Lymphocyte Infusion after Allogeneic Stem Cell Transplantation. 2008.
18. Thakar MS, Forman SJ. ASH evidence-based guidelines: is there a role for second allogeneic transplant after relapse? Hematology Am Soc Hematol Educ Program. 2009:414-8. Accessed at: http://asheducationbook.hematologylibrary.org/content/2009/1/414.long
19. Blau IW, Basara N et al. Second allogeneic hematopoietic stem cell transplantation as treatment for leukemia relapsing following a first transplant. *Bone Marrow Transplant. 2000 Jan; 25(1):41-5.*
20. Michallet M, Tanguy ML et al. Second allogeneic haematopoietic stem cell transplantation in relapsed acute and chronic leukaemias for patients who underwent a first allogeneic bone marrow transplantation: a survey of the Société Française de Greffe de moelle (SFGM). Bone Marrow Transplant. 2000 Jan;25(1):41-5.
21. Tomonari A, Iseki T et al. Second allogeneic hematopoietic stem cell transplantation for leukemia relapse after first allogeneic transplantation: outcome of 16 patients in a single institution. Int J Hematol. 2002 Apr;75(3):318-23.
22. Gupta, V, Richards, S, Rowe, J. Allogeneic, but not autologous, hematopoietic cell transplantation improves survival only among younger adults with acute lymphoblastic leukemia in first remission: an individual patient data meta-analysis. *Blood*. 2013 Jan 10;121(2):339-50.

Professional Society Guidelines

23. National Marrow Donor Program® (NMDP) and the American Society for Blood and Marrow Transplantation (ASBMT) referral guidelines: Recommended Timing for Transplant Consultation. Accessed at: https://bethematchclinical.org/Transplant-Indications-and-Outcomes/Referral-Timing-Guidelines/
24. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Acute Lymphoblastic Leukemia. V1.2018. Accessed at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp
    - The American Society for Blood and Marrow Transplantation (ASBMT). Accessed at: http://www.asbmt.org/?page=GuidelineStatements
    - The Role of Cytotoxic Therapy with Hematopoietic Stem Cell Transplantation in the Treatment of Adult Acute Lymphoblastic Leukemia: Update of the 2006 Evidence Based Review. Biol Blood Marrow Transplant. 2012;18:18-36.
25. The Role of Cytotoxic Therapy with Hematopoietic Stem Cell Transplantation in the Treatment of Acute Lymphoblastic Leukemia in Children: update of the 2005 evidence-based review. Biol Blood Marrow Transplant. 2012; 18(4):505-522. National Marrow Donor Program® (NMDP). Patient Eligibility for HCT. Accessed at: https://bethematchclinical.org/Transplant-Indications-and-Outcomes/Eligibility/
26. National Cancer Institute.
    - Adult Acute Lymphoblastic Leukemia PDQ 2018. Accessed at: http://www.cancer.gov/cancertopics/pdq/treatment/adultALL/HealthProfessional/page1
    - Childhood Acute Lymphoblastic Leukemia PDQ 2018. Accessed at: http://www.cancer.gov/cancertopics/pdq/treatment/childALL/HealthProfessional
27. National Bone Marrow Donor Program. Measuring Engraftment. Accessed at: http://marrow.org/Patient/Transplant_Process/Days_0-30/Measuring_Engraftment.aspx
28. Bredeson C, Varela NP, Walker I, Kuruvilla J, Kouroukis CT, Stem Cell Transplant Steering Committee. Stem cell transplantation in the treatment of acute lymphoblastic leukemia. Toronto (ON):

Cancer Care Ontario (CCO); 2016 Feb 1. 37 p. Accessed at: http://www.guideline.gov/content.aspx?f=rss&id=50087&osrc=12

Other Resources

29. McKesson InterQual Criteria for Procedures: Adult 2017 InterQual Transplantation, Allogeneic Stem Cell; 2017.
30. DynaMed LLC [website]. EBSCO Publishing 1998-2018. Acute Lymphoblastic Leukemia.
31. UpToDate. [website]. Waltham, MA: Walters Kluwer Health; 2018.
    - Larson R. General principles of hematopoietic cell transplantation for acute lymphoblastic leukemia in adults.
    - Horton TM, Steuber CP. Risk group stratification and prognosis for acute lymphoblastic leukemia in children.
    - Larson R. Induction therapy for Philadelphia chromosome positive acute lymphoblastic leukemia in adults.
    - Larson R. Treatment of relapsed or refractory acute lymphoblastic leukemia in adults.
    - Holmberg L, Deeg H, Sandmaier B. Determining eligibility for autologous/allogenic hematopoietic cell transplantation.
    - Stock W, Estrov Z. Detection of minimal residual disease in acute lymphoblastic leukemia.
32. Advanced Medical Review (AMR): Policy reviewed by MD board certified in Internal Medicine, Oncology, Hematology. October 8, 2012

Review/Revision History:

10/31/2012: Policy created
7/29/15: The policy was reviewed and updated with revisions made to the pre-transplant criteria, minor revision to the criteria to include any stage of relapse, guideline and reference sections were updated.
12/14/16, 6/22/17: Policy reviewed, no changes
9/13/18: Policy reviewed, no changes to criteria, updated guidelines and references.